Exhibit 3

Tertiary patenting on drug–device combination products in the United States

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Drug–device combination products are becoming increasingly prevalent, with many lasting years beyond the expiration date of primary and secondary patents on the drug itself.

The epinephrine autoinjector (EpiPen) treatment for anaphylaxis has been making headlines since 2016 for price increases of over 400%, even though epinephrine was isolated over 100 years ago[1–4]. Investigations by the United States Congress have revealed the primary reason for such price increases: there are four patents on epinephrine's special delivery device that do not expire until 2024 (ref. 5). These patents have made it impossible for other manufacturers to copy the EpiPen delivery system, preventing low-cost generic competition. Patents only last 20 years, but 2024 would mark 37 years since the EpiPen was approved for marketing in the United States in 1987.

Other drug–device combinations like the EpiPen are protected by patents on the drug delivery devices. One survey of patent data on a sample of 49 combination products for asthma, chronic obstructive pulmonary disease, diabetes, and anaphylaxis found that over half of the current patents were directed to the device itself[6]. Such patents allow manufacturers to raise prices by blocking generic competition in those markets[7–10]. One study of insulin pens found that the number of patents listed with the US Food and Drug Administration (FDA) on these combination products more than doubled between 2004 and 2014, coincident with an increase in prices on the products[11].

It is unknown how common drug delivery device patents are across all drug classes. To assist policymakers in understanding the causes for, and solutions to, high drug prices, and in updating and modernizing approaches to regulation of combination products[12], we sought to evaluate the prevalence of drug delivery device patents in the United States and the extent to which they block potential low-cost generic competition (**Box 1**). Since drug delivery devices can be updated and repatented incrementally (e.g., different components on an injector pen), we expected to find more drug delivery device patents to accrue over time, and consequently, to expire later than other kinds of patents.

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RESULTS

In the four years covered in our study, we found 1,784 distinct drug products associated with one or more patents, and 5,056 patents in total. About 7% (369) of these were tertiary patents and were associated with 144 drug–device combination products. The most common such products were inhalers (31%, 45/144), injector pens (24%, 34/144), and patches (18%, 26/144). These 144 products could be traced to 66 different manufacturers, with most coming from GlaxoSmithKline (9%, 13/144), AstraZeneca (6%, 9/144), Eli Lilly (6%, 9/144), Novo Nordisk (6%, 9/144), and Novartis (6%, 8/144). **Supplementary Table 1** includes our full product sample and the relevant descriptive characteristics of these products and patents.

Changes in prevalence of primary, secondary, and tertiary patents over time. The proportion of patents classified as tertiary patents tripled from 3% (27/916) in the year 2000 to 9% (295/3,464) in 2016. Among all drug products associated with one or more patents, the proportion with a device patent increased from 3% (18/614) in the year 2000 to 10% (109/1,135) in 2016 (**Table 1**).

In 2000, there were 42 drug–device combination products (among 614 total drugs) and 85 associated patents. These 85 patents included 3 (4%) primary patents, 53 (62%) secondary patents, and 29 (34%) tertiary patents. A median of two patents (interquartile range, IQR: 0 to 4) were cited per drug–device combination product.

In 2005, there were 68 drug–device combination products (among 835 total drugs) and 179 associated patents. These 179 patents included 9 (5%) primary patents, 109 (69%) secondary patents, and 61 (34%) tertiary patents. A median of two patents (IQR: 1 to 4) were cited per drug–device combination product.

In 2010, there were 95 drug–device combination products (among 997 total drugs) and 416 associated patents. These 416 patents included 29 (7%) primary patents, 197 (47%) secondary patents, and 190 (46%) tertiary patents. A median of three patents (IQR: 2 to 6) were cited per drug–device combination product.

In 2016, there were 127 drug–device combination products (among 1,135 total drugs) and 844 associated patents. These 844 patents included 64 (8%) primary patents, 302 (36%) secondary patents, and 478 (57%) tertiary patents. A median of four patents (IQR: 2 to 11) were cited per drug–device combination product.

Reasons for changes in tertiary patent prevalence. We observed three major factors contributing to the increasing prevalence of tertiary patents. First, tertiary patents played a growing role in combination products' patent portfolios (**Fig. 1**). This change was driven in part by a growing number of products listing only tertiary patents and no other patents covering the drug. Overall, 22% (32/144) of the products listed only tertiary patents during any of the years in which they were being actively marketed. The number products only citing tertiary patents climbed from 21% (9/42) in

Table 1 Proportion of tertiary patents relative to all patents and all patented products

Year	All patents	Tertiary patents, *N* (%)	All drug products listing one or more patents[a]	Drug products listing a drug delivery device patent, *N* (%)[a]
2000	916	27 (3)	614	18 (3)
2005	1,593	61 (4)	835	35 (4)
2010	2,069	135 (7)	997	59 (6)
2016	3,464	295 (9)	1,135	109 (10)

[a]Products were counted by new drug application (NDA) numbers.

2000 to 22% (15/68) in 2005 to 22% (21/95) in 2010, and to 25% (32/128) in 2016.

Second, a growing subset of products listed high numbers of tertiary patents. In 2000, only 4 drug–device combination products (out of 42, 10%) cited 3 such patents. By 2016, 53 (out of 127, 41%) listed 3 or more, and 17 (13%) listed 10 or more. For example, the autoinjector Evzio (naloxone) for treating opioid overdoses and Auvi-Q (epinephrine) each cited more than 20 tertiary patents in 2016.

Third, the same products accrued more drug delivery device patents over time. Of the 144 products in our main sample, 94 (65%) were marketed during two or more of the four time points we studied. Of those 94 products, 47 (50%) did not have a tertiary patent listed in the first year it appeared in our database but did have one listed in a later year. Over half (59%, 55/94) had more tertiary patents listed in a later year than in an earlier one. For example, Sumavel DosePro (sumatriptan injection) for migraine headaches had three tertiary patents in 2010, but nine by 2016. In other cases, modified formulations were introduced as new product lines with novel trade names, bearing more tertiary patents. For example, AstraZeneca's Pulmicort Respules (budesonide inhalation suspension) had one tertiary patent in 2005 and none in 2010, while its newer Pulmicort Flexhaler (budesonide inhalation powder) appeared in 2010 with two tertiary patents.

Last-expiring patents on drug–device combination products. Tertiary patents were the last to expire in 70% (101/144) of the sample, expiring a median of 4.7 years (IQR: –0.5 to 11.6) after all others. Among the 144 products were 31 that exclusively listed tertiary patents. These products had been on the market for a median of 15.2 years (IQR: 6.1 to 20.7). These products' last-expiring tertiary patents ended a median of 16.5 years (IQR: 12.7 to 19.7) after FDA approval.

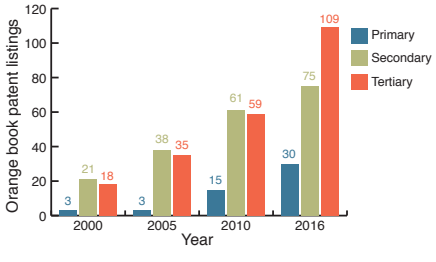

Figure 1 Changes in prevalence of primary, secondary, and tertiary patents over time. By 2016, the number of tertiary patents for drug–device combination products in the Orange Book had overtaken those of other patent types.

Among the 144 products in the main sample, 113 had tertiary device and other non-device (primary or secondary) patents available for comparison of their expiration dates. These 112 products were relatively newer and were approved a median of 11.2 years ago (IQR: 4.9 to 16.9). These products' last-expiring tertiary patent was a median of 16.5 years (IQR: 13.0 to 21.6) after FDA approval as compared to a median of 15.2 years (IQR: 12.3 to 18.3) for all other patent types. This difference was most pronounced among the 22 injector pens with a median difference of 6.6 years (IQR: 3.8 to 10.1) as compared to a median difference of 1.4 years (IQR: –1.8 to 5.2) among the 42 inhalers and of 0.0 years (IQR: –1.7 to 4.2) among the 20 patches.

Among these 113 drugs, 32 had all three patent types available for comparison of their expiration dates. There was a median of 12.4 years (IQR: 9.9 to 15.0) between those products' FDA approvals and the expiration of the last-expiring primary patent, a median of 0.2 additional years (IQR: 0.0 to 4.8) to the expiration of the last secondary patent, and a median of 4.4 additional years (IQR: –1.8 to 7.3) to the expiration of the last tertiary patent.

Three overlapping layers of patent protection on drug–device combinations. **Figure 2** shows the differences in patent counts and their expiration dates relative to FDA approval for all patents by type for the 42 drug–device combination products in 2000 as compared to the 127 drug–device combination products in 2016. For these products, by 2016, tertiary patents outnumbered and outlasted secondary patents (which in turn outnumbered and outlasted primary patents); by contrast, in 2000, secondary patents were more prevalent.

DISCUSSION

Patents listed with the FDA related to drug delivery devices have more than tripled since 2000. These tertiary patents, as we have labeled them, contributed a median of 4.7 years of additional patent protection for drug–device combination products beyond the primary and secondary patents, with such market exclusivity extensions being particularly common among pens and inhalers. In 2016, 32 drug products were covered exclusively by tertiary patents.

Our finding that tertiary patents are being listed in the Orange Book[5] and that they typically expire later than other patent types implies that for these products, generic versions are prevented from entering the market for longer than would otherwise be the case. If manufacturers could not list drug delivery device patents in the Orange Book, the median product in our sample would have had 13.9 years (IQR: 3.2 to 17.1) of patent life remaining after FDA approval, as compared to the current situation in which the median is 17.3 years (IQR: 14.8 to 22.2). Aside from the difference of 3.4 years between these scenarios, the removal of device patents from the Orange Book would immediately clear the FDA to review applications from generic companies for 38 drugs in 2016. These factors increase the risk that such drugs will be subject to price increases.

Generic manufacturers seeking FDA approval before the expiration of tertiary patents must make a special certification (known as a "Paragraph IV certification") that the reference product's patents are either irrelevant or invalid (**Supplementary Table 2**). Other studies have found that such patent challenges are undertaken less frequently for products in smaller, more specialized markets and consequently lead to longer market exclusivity periods[13]. We note that only 22% (32/144) of the drugs in our sample appeared on the FDA's list of drugs with a patent challenge, while a generic therapeutic equivalent was listed in the Orange Book for only 12. By contrast, such patent challenges are the norm for blockbuster drugs. Thus, drug–device combination products covered by tertiary patents may face fewer patent challenges and even weak tertiary patents may go unchallenged in these markets and successfully delay FDA approval for many years.

Another implication of our study is that manufacturers appear to be continuously modifying and repatenting the designs of drug delivery devices for combination drug–device products. While some of these changes may have therapeutic value, they also may increase the risk of product recalls, manufacturing errors, and device failures, as well as require re-education of physicians and patients in how to use the updated device. For example, GlaxoSmithKline's Ventolin HFA (albuterol sulfate) inhaler was recently recalled for a leaky

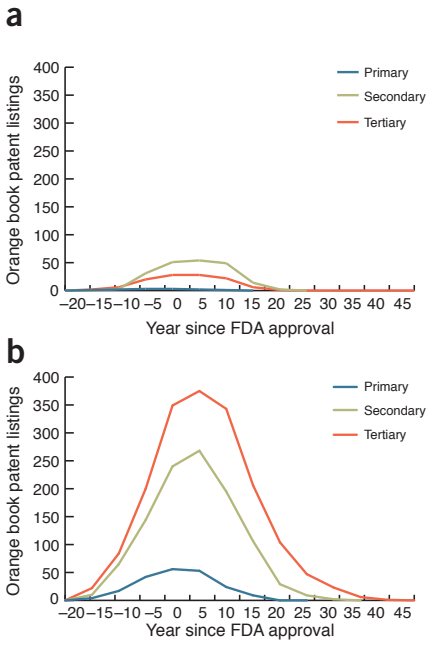

Figure 2 Duration of unexpired primary, secondary, and tertiary patents for drug–device combination products in 2000 and 2016 (relative to FDA approval date). (**a**) Breakdown of Orange Book patents for 42 drug–device combination products in 2000. (**b**) Breakdown of Orange Book patents for 127 drug–device combination products in 2016.

canister, a component of the device covered by many Orange Book–listed patents[14]. Similarly, GlaxoSmithKline's Advair Diskus (fluticasone propionate and salmeterol inhalation powder) was recently recalled owing to problems relating to the device delivering fewer doses than was indicated on the dose counter, a patented subcomponent of the device[15]. Other products captured in our study with recalls flagged by the FDA as having "defective delivery systems" also include Tudorza Pressair (aclidinium bromide inhalation powder), Qnasl (beclomethasone dipropionate), Combivent Respimat (ipratropium bromide and albuterol), Auvi-Q, and the Epipen[16,17].

A number of policy options could be appropriate for this area. One possible approach would be to confine sponsors to listing patents in the Orange Book only at the time of filing their initial application with the FDA. This would restrict companies from adding patents on a rolling basis to the Orange Book without simultaneously providing clinical trials to support product changes. Another option is to make Orange Book patent listing more selective by making only primary patents listable or barring the listing of device patents entirely. Other countries have established patent review bodies within their drug regulators to ensure that newly listed patents cover product changes that confer additional clinical benefit, which is not among the legal criteria for obtaining the patent in the first place[18].

Our study was limited in that our methodology relies upon tertiary patent listings to identify combination products. Consequently, we may not have captured combination products without patents or those that have only listed non-device patents. The FDA does not currently maintain a list of drug–device combination products nor does it have a field within its current databases that indicate such combinations[19]. However, a previous study searched by products' active ingredients, rather than using device patents to locate combination products, and we found that it was nearly universal for combination products to include at least one device patent[6].

Other factors not observed by this study may also contribute toward the apparent proliferation of tertiary patents or lack of generic competition in drug–device combination markets, such as those related to the specialized nature of these markets and challenges in determining interchangeability between two different devices delivering the same drug. The absence of generic insulin in the United States, for example, is clearly affected by fac-

Box 1 Methods

Brand-name drug manufacturers are required by law to list in the FDA's *Approved Drug Products with Therapeutic Equivalence* register (the "Orange Book") patents that they consider essential in protecting their prescription drug products. We obtained electronic copies of the Orange Book's[5] 'patent' and 'product' tables from the FDA for the years 2000, 2005, 2010, and 2016. These provide four snapshots in time of the small-molecule drug market with respect to the products available (brand-name and generic) and with respect to the patents protecting brand-name products. Because the FDA considers drug delivery devices to be inseparable from the medicines that they contain, manufacturers are permitted to list in the Orange Book patents covering such devices along with patents on the drug active ingredient and other patents on the drug itself, such as the crystal structure, salt, and methods of use[10]. We linked patent numbers listed in the Orange Book for each of the four years to LexisNexis TotalPatent, an international patent database, and extracted patent titles, abstracts, and claims (http://www.lexisnexis.com/totalpatent/signonForm.do).

For each patent, we used a two-step screening procedure to code them as covering drug delivery devices or the drug itself. The first step was to screen for device patents by reviewing each patent's title and abstract, which was followed by full text review when necessary to confirm device designations. Drug delivery device patents were those that described a device, implement or encasing (or a part thereof) used to deliver, preserve, distribute, dispense, or properly apply or ingest the medicament in the correct dosage and/or at the correct time.

Among non-device patents, we extracted the data from the electronic Orange Book 'substance patent' field, which indicates whether the manufacturer considers the patent in question to be integral to the drug's active ingredient. We coded these active-ingredient-related patents as 'primary patents'. The remaining patents therefore pertained to more peripheral aspects of the drug, including its formulation (e.g., extended release) or its indications. We coded these as 'secondary patents'. Since drug delivery device patents are even more peripheral than secondary patents on the drug itself, we designated these as 'tertiary patents'.

From the Orange Book, we imported into our database essential information about the products, including the trade names, active ingredients, strengths, dosage forms, routes of administration, manufacturers, marketing status (discontinued vs. actively marketed), and approval dates. We included all products with a tertiary patent cited at any time point in our study in which the product was being actively marketed (i.e., it had not been discontinued). In doing so, our data still captured products' patent portfolios before and after the expiration of any tertiary patent listings (i.e., some products had tertiary patent listings for some time points in our study, but not others).

Our analysis included a tabulation of the counts of each of the three patent types (primary, secondary, tertiary) by product and collectively across the sample for each year in our study. We also assessed the number of years between FDA approval and the last-expiring patent of each type by product and collectively for each time point. Another variable considered was the current age of products (i.e., the years between FDA approval and January 1, 2017).

tors other than the tertiary patents or even patents on the insulins themselves[20]. Still, we found that these manufacturers continue to redevelop and repatent their pen delivery devices. As another example, the FDA mandatory switch away from ozone-depleting emissions from inhalers—a process which has been negotiated and introduced progressively since 1997 (ref. 21)—may have contributed to some extent to manufacturers' device design updates. Nonetheless, companies have continued to update these devices well after that time.

Finally, some patents (regardless of type) were cited by multiple products. To reduce double-counting, we have reported statistics on the unique number of patents as well as the number of product–patent combinations listed.

Conclusions

The practice of listing tertiary patents for combination products in the Orange Book is accelerating. As tertiary patents may be added progressively over time, they may extend patent life well beyond the life of all other patents and substantially delay competitors from gaining FDA approval, which makes these markets especially vulnerable to high prices. Should reform be considered, options include limiting the types of listable patents in the Orange Book. Similarly, any product that is different enough from the reference product to earn a new patent could require more explicit clinical evidence to demonstrate its safety and efficacy. These measures would discourage excessive redevelopment and repatenting of drug–device combination products, and open markets to lower-cost generics sooner.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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